alternative under, 35 U.S.C. §103(a) as being obvious over Gandorfer et al. (Br J Ophthalmol 2001; 85:6-10). Claims 1-10, 13-21 and 24-28 stand rejected under 35 U.S.C. §102(b) as anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Trese et al. (American Academy of Ophthalmology, ISSN 01610-6420). Lastly, claims 1-10, 13-21 and 24-28 stand rejected under 35 U.S.C. §102(a) as anticipated by, or in the alternative, under, 35 U.S.C. §103(a) as obvious over Shi et al. (Graefe's Arch Clin Exp Ophthalmol (2002) 240:46-62).

Remarks Directed to Rejection of Claims 1-4, 7-10 and 13 under 35 U.S.C. §102(b)/§103(a) with Respect to Gandorfer et al.

Independent claim 1 at lines 3-4 recites the limitation of "delivering a dose of a plasmin composition of less than 0.4 units in a composition of about 0.1 cubic centimeters into a vitreous body of a subject human eye."

In contrast to the invention of claim 1, Gandorfer et al. teaches injection of one or two units per 0.1 ml of plasmin being injected into the vitreous cavity of 24 freshly slaughtered pig eyes. (See page 6, abstract: methods). Gandorfer teaches that:

> Eyes exposed to 1 U[nit] plasmin for 30 minutes had a dense network of residual collagen fibrils while those exposed to 1 U[nit] plasmin for 60 minutes had only sparse collagen fibrils covering the ILM [inner limiting membrane]. Eyes treated with 2 U[nit] plasmin for 60 minutes had a smooth retinal surface, consistent with a bare ILM. . . . The degree of vitreoretinal separation depends on the concentration and length of exposure to plasmin. (Page 6, abstract: results and conclusion).

Applicant submits that the invention of claim 1 is not anticipated by Gandorfer et al. on the basis that Gandorfer et al. fails to teach the limitation of "delivering a dose of plasmin composition of less than 0.4 units in a volume of about 0.1 cc." Additionally, the inventive process according to claim 1 recites plasmin delivery into the vitreous body of a "subject human eye." As Gandorfer et al. nowhere teaches plasmin delivery in an amount of less than

one unit per 0.1 ml and into an eye other than that of a pig, it is respectfully submitted that Gandorfer et al. does not anticipate independent claim 1 or the claims that depend therefrom. Additionally, the limitations of pending claims 3, 4, 7 and 8 are nowhere found in Gandorfer et al.

In light of the above remarks, the rejection of claims 1-4, 7-10 and 13 under 35 U.S.C. §102(b) as anticipated by Gandorfer et al. is believed to be improper and it is respectfully requested that it be withdrawn.

Applicant submits that Gandorfer et al. teaches away from the invention of claim 1 and as such cannot render the pending claims obvious. Gandorfer et al. in the abstract: results makes clear that one unit of plasmin for 30 minutes is inadequate to produce a clean inner limiting membrane while one unit of plasmin in contact with the vitreous for 60 minutes showed only sparse residue and two units of plasmin for 60 minutes achieved the desired smooth retinal surface. It is respectfully submitted that one skilled in the art upon reading Gandorfer et al. must conclude according that there is a direct correlation between the concentration and exposure time of plasmin and the degree of vitreoretinal separation. (Page 6, abstract: results). The concentration of Gandorfer indicating that one unit of plasmin is inadequate to exact complete vitreoretinal separation even after 60 minutes. Thus, Gandorfer et al. teaches the usage of plasmin concentrations of greater than two units per 0.1 ml in order to exact vitreoretinal separation in times shorter than 60 minutes.

In contrast to Gandorfer et al., claim 1 recites a plasmin composition dosage of less than 0.4 units to create vitreal liquefaction. It is respectfully submitted that one skilled in the art upon reading Gandorfer et al. must conclude that the usage of less than 0.4 units of plasmin would either never completely induce vitreoretinal separation or do so if at all, on a time scale of hours or days. As a result, Applicant submits that Gandorfer et al. teaches away

from the invention of claim 1, or in the alternative, that exacting vitreal liquefaction with less than 0.4 units of plasmin represents a surprising result thereover.

In addition, the limitations of dependent claims 3, 4, 7 and 8 are nowhere found or contemplated in Gandorfer et al. Since a rejection under 35 U.S.C. §103(a) must consider all claim limitations, especially when these limitations are lacking in the prior art, these limitations represent an independent basis for the allowability of these dependent claims.

In light of the above remarks, the rejection of claims 1-4, 7-10 and 13 under 35 U.S.C. §103(a) as being obvious over Gandorfer et al. is believed to no longer be proper and it is respectfully requested that it be withdrawn.

Remarks Directed to Rejection of Pending Claims
under 35 U.S.C. §102(b)/§103(a) over Trese et al.

Trese et al. is cited for teaching the "delivery of autologous human plasmin into a vitreous body of an eye and then incubating the eye, and further delivering a plasmin inhibitor, wherein the dose of plasmin is between 0.1 and 1.0 units of plasmin." (Paper No. 8, page 3, paragraph 5).

In response to these rejections, the Supplemental Declaration of Michael K. Hartzer, an author of Trese et al. as well as an inventor of the pending application, is offered to show through experimental data that the active substance used in Trese et al. is predominantly a streptokinase-plasminogen complex and not plasmin itself. This Supplemental Declaration corrects a previous statement that the complex was streptokinase-plasmin. The conclusion of the Supplemental Declaration of Michael K. Hartzer is that the streptokinase-plasminogen complex which at the time of Trese et al. was thought to be plasmin had a lower activity to induce vitreal liquefaction and therefore the conclusion that 0.4 units of plasmin did not produce reliable liquefaction. The declaration of a highly skilled practitioner in the art, Professor Patrick J. Gaffney, is also submitted to support this position. In light of the

appended Supplemental Declaration of Michael K. Hartzer and the Declaration of Professor Patrick J. Gaffney, it is submitted that Trese et al. fails to teach the recited claim limitation of delivering less than 0.4 units of a plasmin composition to induce vitreal liquefaction and therefore it is submitted that rejection of the pending claims under 35 U.S.C. §102(b) as being anticipated by Trese et al. is no longer proper and it is requested that it be withdrawn.

Trese et al. is submitted to not render the pending claims obvious on the basis of the statements made on page 1610, first column, first full paragraph, that read in relevant part

> The dose of 0.4 IU of autologous plasmin enzyme, which seems optimal for producing a PVD [posterior vitreous detachment] in humans, does not show the reliable liquefaction of vitreous that was seen in animals. This suggests to us that a vitreous cutter is still necessary to safely remove the partially liquefied vitreous, making space for gas used in the postoperative management of stage 3 macular holes. We believe that this study demonstrates that it is possible to achieve spontaneous posterior vitreous separation and closure of macular holes in the human eye but that liquefaction of the vitreous gel is variable in human eyes at the dose of 0.4 IU.

Applicant submits that Trese et al. teaches away from the recited claim limitation of using less than 0.4 units plasmin composition per independent claims 1 and 14 to achieve vitreal liquefaction on its face and without consideration of the fact that Trese et al. actually used a streptokinase-plasminogen complex.

In addition, the subject matter of dependent claims 3, 4, 7, 16, 17 and 18 is nowhere taught or contemplated in Trese et al. Since all claim limitations must be considered especially when lacking in the prior art, this represents an independent basis for the nonobviousness of these pending claims relative to Trese et al.

In light of the above remarks, the Supplemental Declaration of Michael K. Hartzer, and the Declaration of Professor Patrick J. Gaffney, it is submitted that the rejection of the

pending claims under 35 U.S.C. §102(b)/§103(a) is no longer proper and it is respectfully requested that it be withdrawn.

Remarks Directed to Rejection of Pending Claims under 35 U.S.C. §102(a)/§103(a) over Shi et al.

Applicant herein incorporates by reference the remarks of record with respect to the rejection of pending claims under 35 U.S.C. §102(a).

The Supplemental Declaration of Michael K. Hartzer is offered under 37 CFR 1.131 for the purpose of showing reduction of the present invention to practice prior to publication of Shi et al. As Shi et al. is therefore not prior art to the present invention, withdrawal of any rejection of the pending claims thereover is requested.

Summary

Claims 1-10, 13-21 and 24-28 are the claims pending in this application. Each pending claim is believed to be in proper form and directed to allowable and patentable subject matter. Reconsideration of the rejections and the allowance of the pending claims is solicited. If the Examiner finds to the contrary, it is respectfully requested that the undersigned in charge of this application be called at the telephone number given below to resolve any remaining issues.

Respectfully submitted,

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I hereby certify that this paper or fee (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service "Express Mail Post Office To Addressee" Service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Janice R. Kuehn